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ERG components of negative polarity from the inner retina and the optic nerve response

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Key words: proximal retina, electrical stimulation, ERG, optic nerve response, PhNR, PNR, STR

Abstract

ERG components of negative polarity in the light-adapted and in the dark-adapted inner retina are reviewed from a clinical perspective and include consideration of experimental research. Field potentials are inherently complex including summing contributions from specialized neurons as well as from glial elements. This property applies to the PERG, PhNR and to the STR. Experimental research can contribute to identifying the sites/cells of origins i.e. by determining depth profiles and by pharmacological manipulation. Intraretinal microelectrode-studies and pharmacological dissection of light-evoked responses have elucidated the origin of field potentials from the retinal pigment epithelium to the retinal ganglion cells. Thresholds for dark-adapted response components have been compared. Attenuation of the STR by anesthesia was found in cats *in vivo* when compared to threshold intensities used in isolated eye preparations *in vitro*, suggestive of depression of inner retinal activity by anesthetics. Evidence has been presented for antidromically elicited retinal responses of negative polarity that resemble the STR and summate with the light-evoked retinal response. This observation supports the notion that negative field potentials and components as recorded in the vitreous and at the cornea receive contributions from retinal ganglion cells. The weight of this contribution appears to vary among species, at least concerning the STR. The ocular negative responses from the inner retina are compared to cortical excitatory mechanisms generating negativity in the baseline of the EEG.

In the light of an increasing interest in assessing the function of the inner retinal layers, I shall briefly review the responses and components of negative polarity that are generated in the inner retina. For a detailed background of these signals, which largely reflect various aspects of ganglion cell and amacrine cell activity, the reader is referred to [1–3]. Clinically accessible signals of this sort are shown in a cartoon (Figure 1) and, together with experimentally characterized responses listed in Table 1. I shall also review the properties of the optic nerve action potential including previously unpublished data obtained by antidromic electrical stimulation, which generates retinal field potentials of negative polarity as well.

Clinically accessible signals

Scotopic Threshold Response, STR

Among the clinically accessible signals embedded as components in the electroretinogram (ERG), I first address the scotopic threshold response, STR (Figures 1–3). The STR is a rod-driven response to very weak stimuli under full dark adaptation [4]. The signal is sensitive to very dim levels of background light [5, 36] appearing with stimuli below the threshold intensity for the b-wave, and generating measurable amplitudes about 1.0 units above the psychophysical threshold (summarized in Figure 5). In a recent study, Jost found a difference of 0.99 log units between

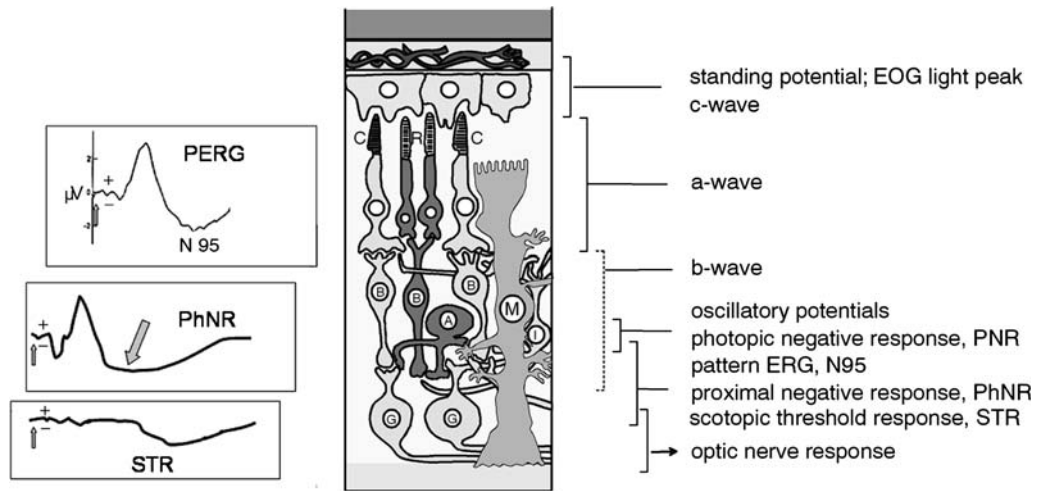


Figure 1. Cartoon of mammalian retina, of selected signals from the retina and approximate sites of generation of ERG components. Note that proximal negative responses (PNR) and optic nerve responses (ONR) are obtained in experimental situations. Vertical arrows indicate the stimulus.

the STR recorded and the psychophysical threshold using the same Ganzfeld stimulator for both [6]. Due to processes of amplification from photo-

receptors to third order neurons [37] and mechanisms of inner retinal network adaptation the STR can reflect remaining sensitivity in advanced

Table 1. Overview of signals of negative polarity from inner retina and optic nerve

Response/ERG component	Abbreviation	Species; stimulus conditions	Characteristics	References*
<i>Clinically accessible</i>				
Scotopic threshold response	STR	cat, rat, mouse, monkey, human full dark adaptation	rod-driven signal	[4–11]
Pattern ERG, N 95 component	PERG	cat, human. Light –adapted,	spatially tuned	[12–16]
Photopic negative response in cone ERG	PhNR	monkey, human	presumed cone-driven ganglion cell activity	[17]
<i>Experimentally assessed</i>				
TTX-sensitive component in multifocal ERG	mfERG	monkey	Presumed ganglion cell-generated component in mfERG	[18]
M-wave	M-wave	Amphibian (necturus), cat. Light-adapted focal intraretinal signal, extra cellular microelectrode	spatially tuned, presumed glial response from inner retina	[19, 20]
Proximal negative response	PNR	toad, pigeon, turtle dog, cat, monkey. Light-adapted inner retinal spatially tuned signal, extracellular microelectrode	presumably amacrine cell-driven signal	[21–23]
Optic nerve response	ONR	Cat, dog, rabbit. Compound action potential of optic nerve <i>in vitro</i> , perfused eye or superfused eye cup	rod and cone-driven composite “output” signal from isolated eyes	[24–33]
Antidromic electrical retina response	ERR	Cat eye <i>in vitro</i> . Electrical stimulation of optic nerve	antidromically elicited retinal field potential resembling and revealing summation with the STR	[11, 28, 34]

*only selected references could be included in this brief overview.

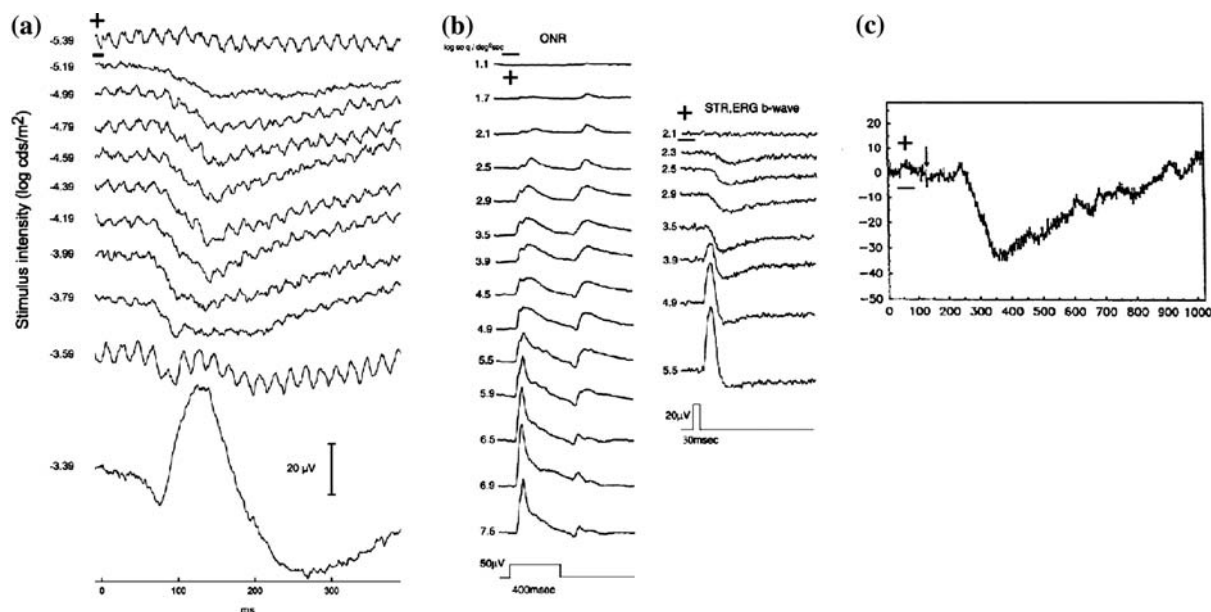


Figure 2. Typical traces of scotopic threshold responses. (a) human STR intensity series recorded with a DTL fibre electrode from a 30 yr old volunteer, average of 4, with the STR appearing at an intensity of $-5.19 \log \text{cd.s/m}^2$ from [6]. (b) intensity series of ERGs (right column) and optic nerve responses (left column) recorded from an *in vitro* arterially perfused mammalian eye (from [5] by permission). For the ONR recordings longer pulses were used in order to analyze/observe the OFF-components. (c) Average of STR recordings from 5 healthy fully dark adapted rats (R. Bush and G. Niemeyer, unpublished; [35]).

inherited degeneration of the retina [7] when the a- and b-waves of the ERG have vanished. We observed that the STR is sensitive to general anesthesia (Figure 20 in [6]): the threshold in the anaesthetized cat was on average 1.25 log units above the threshold intensity for the STR in the isolated perfused cat eye. Examples of human, anesthetized rat and cat (*in vitro*) STRs are shown in Figure 2. The STR thus represents an exquisitely sensitive tool for selective monitoring of rod function in clinical as well in research settings [38–40].

The generation of the STR comprises the complex rod circuit involving four classes of amacrine cells [41] in addition to ganglion cells and Müller cells. The reciprocal synapses of amacrine- to bipolar cells are likely to be sites of signal amplification in the inner retina [37]. The multifold contributions to the STR can be deduced from two studies that addressed loss of the ganglion cells: Sieving [38] reported only changes in configuration and in timing of the STR in cats up to 21 months after sectioning the optic nerve with histologically identified loss of ganglion cells and corresponding thinning of the nerve fiber layer. In the same study a patient with long-

standing posttraumatic unilateral atrophy of the optic nerve was examined electrophysiologically. The STR in the affected eye still generated STRs that, however deviated in configuration, amplitude and timing from those recorded in the control eye of the patient. In macaque monkeys, in contrast, loss of ganglion cells and severe visual field defects induced by experimental glaucoma led to attenuation or loss of the STR [40]. The authors conclude that the balance of contributing cells generating the signals in the proximal retina varies greatly among species.

Photopic Negative Response, PhNR

Light-adapted components of negative polarity in the clinical ERG include the Photopic negative response, PhNR, and the N 95 component of the pattern ERG (Figure 1). The single flash Ganzfeld cone-driven (photopic) ERG recorded after 10 min of adaptation to a rod-suppressing background light is a fast signal with a brief a-wave followed by a spike-like b-wave with rigid timing [2]. Following the b-wave a broad trough below the baseline can be seen under standard stimulus conditions, but is best generated using red flashes

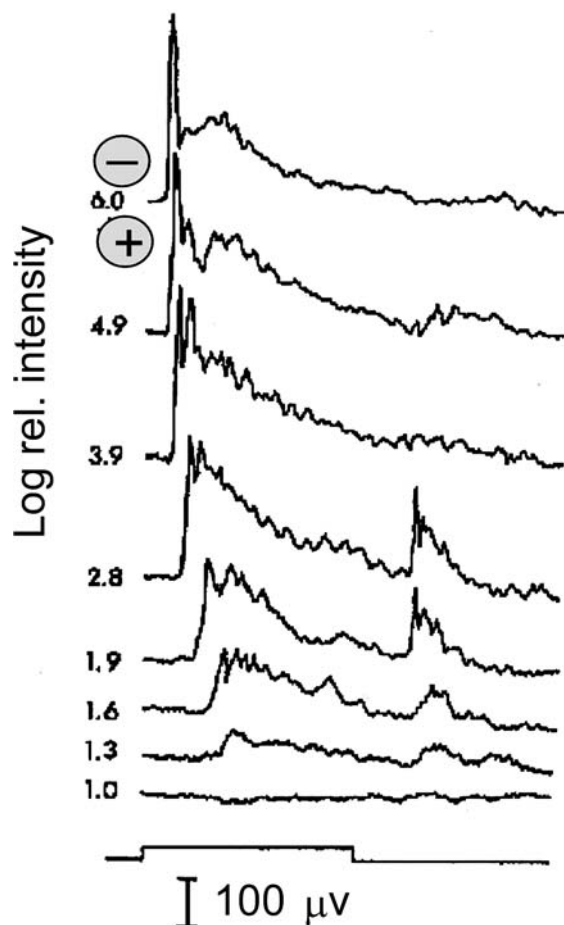


Figure 3. Proximal negative responses (PNR) at recorded by means of a microelectrode in the toad retina at increasing stimulus intensity (bottom to top), modified from [21] with permission. Note that negative polarity is displayed upwards.

presented on a blue background [17]. Experimental evidence [17] and clinical observation in glaucoma and diseases compromising the optic nerve unequivocally show that retinal ganglion cells provide a major contribution to the PhNR. Potentially broad clinical use of this photopic component of the standard Ganzfeld ERG is anticipated.

N 95 component of the pattern ERG

The first comprehensive description [12] and recent reviews [13, 14] document the importance of the pattern ERG (PERG) as a key instrument in assessing the site of visual dysfunction in the axis from photoreceptors to the visual cortex in ophthalmology and neuro-ophthalmology. The

negative component “N95”, a signal of particular diagnostic value is understood to be generated by retinal ganglion cells and related cells responding to stimulation with higher spatial frequencies [15].

Experimentally obtainable signals

TTX-sensitive component of the multifocal ERG

Experimental approaches were and will be necessary to further elucidate the origin of the components underlying the inherently complex field potential, the ERG. A number of signals of negative polarity have been recorded and attributed to inner retinal structures. Using the multifocal ERG (mfERG) in anesthetized monkeys, Hood et al. [18] recorded changes after intravitreal application of micromolar concentrations of TTX, a sodium channel-blocking compound. Comparison of the mfERG before and after the action of TTX revealed a mainly negative component, that could be attributed to ganglion cell and perhaps also to amacrine cell activity.

M-wave: A local ERG component of negative polarity in the inner retina is the M-wave, first recorded and analyzed by Karwoski and Proenza [19] in the amphibian retina. It has been attributed mainly to changes in extracellular concentration of potassium ($[K^+]_o$) as caused by depolarization of the glial Müller cells [42]. The signal was recorded extracellularly by microelectrodes in the inner retina and exhibited spatial tuning. The relatively slow negative response appeared at onset as well as at offset of a light stimulus. Sieving, Frishman and Steinberg [20] were the first to record M-waves in mammalian retina. They used a small spot of light and a white background centered on the tip of the microelectrode at 25% retinal depth. The M-wave could be clearly separated from the intraretinal b-wave (P II) as well as from the faster PNR and from the STR.

Proximal negative response (PNR)

Another experimentally well-established signal in the inner retina is the proximal negative response, PNR, recorded first by Burkhardt [21]

in the amphibian retina (Figure 3). It is a signal of negative polarity recordable near or within the inner retina with spatially tuned flashes centered around the microelectrode. The configuration of the response resembles that of the negative, temporally dispersed optic nerve response (see below) with clear-cut ON- and OFF-components. The signal has been attributed mainly to amacrine cells, which exhibit a synaptic network of particularly high density in the amphibian retina. Dowling and Ripps [22] found that in the skate retina application of TTX failed to greatly affect the PNR and concluded that the signal reflects a depolarization of the resting membrane potential rather than spike-responses of amacrine cells. Ogden [23] reported PNR recordings from monkey and also from chicken, pigeon, turtle and dog, revealing the PNR as a signal generated in all species studied.

The optic nerve response recorded in vitro in relation to the STR

Finally I shall discuss the summed action potential of the mammalian optic nerve as recorded

from the isolated arterially perfused feline eye *in vitro* [24–27]. The *in vitro* perfused isolated mammalian eye preparation affords the opportunity to monitor the summed ganglion cell activity as the output of retinal excitation via a simple Ag–AgCl suction electrode at the severed end of the optic nerve and a surface electrode

(Figure 4a). The typical configuration of the light-evoked temporally dispersed compound action potential at higher stimulus intensity consists of a rapid ON-component, a variable plateau- and a complex OFF-component (Figure 4b). The complexity of this field potential with oscillations at higher stimulus intensities is understood to arise from the integration of the various firing patterns of the different classes of the estimated 193000 axons of retinal ganglion cells [28–31]. The configuration of the responses shown in Figure 4 resembles in polarity, shape and timing the compound action potentials recorded from the optic nerve as well as from within the disc after stimulation of the optic tract of rhesus monkeys [28]. The ONR has a much faster time course than the changes in $[K^+]_o$ that are generated by slow Müller cell

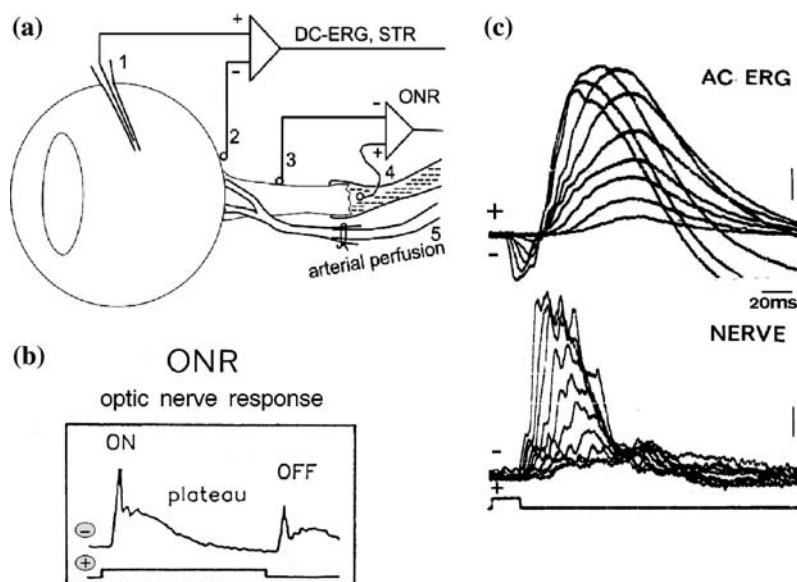


Figure 4. Cartoon of the recording setup of an isolated, arterially perfused feline eye and typical *in vitro* recorded light evoked signals. (a) Setup *in vitro* perfused isolated mammalian eye. 1 and 4: dc electrodes [43], 2 and 3: AgAgCl reference electrodes, 5: PE cannula tied to the ophthalmic artery for perfusion with oxygenated, serum-enriched tissue culture medium at 37.5 °C. (b) Optic nerve response elicited by a submaximal stimulus intensity in dark adaptation, revealing the characteristic components of this temporally dispersed negative compound action potential. (c) superimposed single traces of ERGs (top) and ONRs at increasing intensity in response to pulses of 20 ms in duration under dark adaptation. Calibration bars: 200 μ V for ERG, and 100 μ V for the optic nerve responses.

activity [44]; Niemeyer and Steinberg, unpublished results.

An optic nerve response of similar configuration revealing the different conduction velocities of ganglion cell classes can be elicited by antero-grade electrical stimulation [27, 28]. Several experimental studies have revealed the selective sensitivity of ONR components to pharmacological manipulations [reviewed in 29; 45–49].

ONRs generated by increasing intensities of brief (20 ms) pulses can be compared to ERGs recorded in the same preparation (Figure 4c). At threshold intensities, the ONR was about 1 log unit more sensitive than the STR (Figures 2b, 5), [6, 11, 27].

Values reported for the absolute sensitivity of the STR depend on noise levels as well as on the criterion voltage chosen, and both differ among studies. The relation between the threshold of the ERG as represented by the STR and the ONR is of interest since the signals share the primary generating structure, the retinal ganglion cells. The STR and the ONR both have the same polarity and a similar shape as illustrated in Figure 6: responses to photic stimulation for 400 ms duration have been scaled to the ONR and are displayed with negativity downwards. Note that the long stimulus duration elicited negative OFF

responses in both the ONR and in the STR traces. The latency consistently was found to be longer for the STR than for the ONR. Much like the b-wave, the STR thus is preceded by the summed response of the axons of the retinal ganglion cells. ERG components as field potentials are understood to reflect neuronal as well as slower glial components. This difference in timing has been observed previously [24, 25, 32].

Antidromic electrical stimulation of the optic nerve elicits a negative retinal response

In an attempt to elucidate the negative polarity of the signals discussed here, our laboratory became interested in antidromic electrical stimulation of the ganglion cells via the optic nerve *in vitro* while recording the ERG channel without photic stimulation. Pulses of 1 ms in duration and of 5–15 V were applied to the optic nerve using the electrode configuration described above. Recordings in the ERG channel exhibited a marked stimulus artifact with a barely detectable signal latency due to the short distance of the stimulating electrodes. The artifact was followed by a temporally dispersed signal of negative polarity that resembled the STR. The electrically driven retinal response was saturable

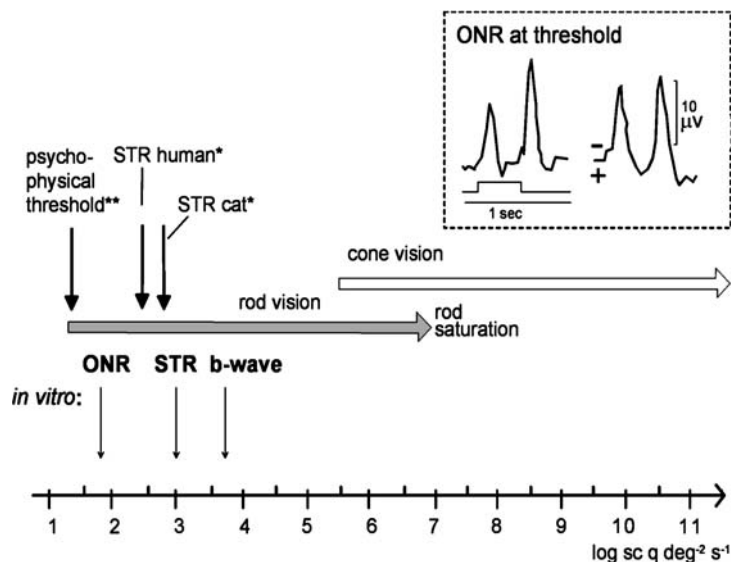


Figure 5. Comparative graph of threshold intensities found to elicit the ERG, STR, and ONR from human, anaesthetized cats (upper half) and from *in vitro* perfused cat eyes (lower half). [§]ONR, optic nerve response recorded *in vitro*. *from Robson and Frishman [8]. **from Finkelstein and Gouras [50]. Inset: ONR traces near threshold recorded in a perfused mammalian eye. Reprinted from [27] with permission from Elsevier.

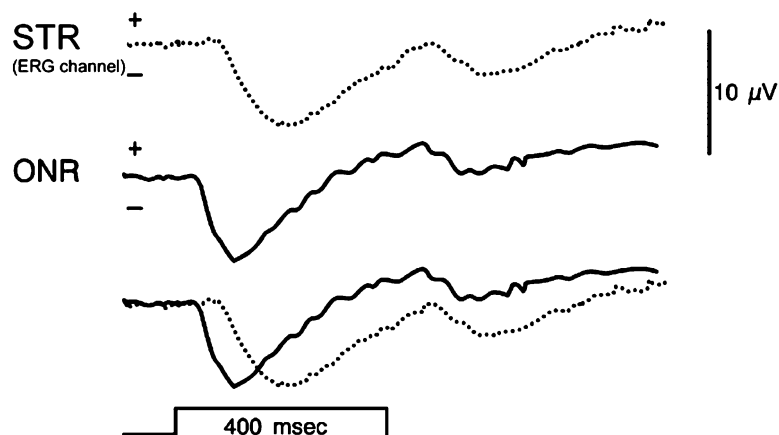


Figure 6. STR traces scaled to the simultaneously recorded ONR of a similar amplitude. The responses were recorded from dark adapted perfused cat eye at very low stimulus intensity and are displayed at the same polarity. The calibration bar refers to the ONR. Recordings were obtained near threshold (white light from xenon source, attenuated by 8.0 log neutral density filters). Average of 32 sweeps, photocell trace below the signals.

when increasing the stimulus strength to about 12 V. More importantly, combination of electrical stimulation with sub maximal photic stimulation revealed summation (Figure 7). These results support the hypothesis that ganglion and amacrine cells in combination with and Müller cells generate field potentials of negative polarity that can be recorded in the vitreous and at the cornea due to passive volume conduction.

An attempt to understand the electrical evoked retinal potential recorded in the perfused eye preparation has to consider the depolarization of Müller cells by stimulation of the optic nerve: Miller, Dacheux and Proenza have shown extra- and intracellular recordings from Müller cells in axolotl following light as well as antidromic electrical stimulation [42]. In fact, the antidromic response recorded near the retinal surface (Figure 2a in [42]) exhibits a configuration similar to the electrically evoked vitreal signal recorded in the perfused cat eye (Figures 6 and 7). The authors conclude that light evoked and antidromically generated depolarizations interact in Müller cells. The corresponding depth profile (Figure 2c in [42]) indicates the origin of the negative field potential in the inner retina and shows a change in polarity near the middle of axolotl retina. This would be in keeping with earlier experimental results of Ogden and Brown [51] who described a “P wave”, a positive response re-

corded intraretinally in cynomolgus monkey near the fovea to transretinal or antidromic electrical stimulation. The depth profile of the P wave exhibits as well negative polarity in the innermost retinal layers (see also review by Karwoski [34]).

Gouras [52] analyzed graded negative potentials in the optic nerve fiber layer of rhesus monkey in the course of identifying phasic and tonic retinal ganglion cells that resemble the antidromically elicited vitreal potentials presented here. Gouras proved the retinal origin of the P wave as opposed to the previously postulated centrifugal origin. Direct comparison of these intraretinal field potentials to the vitreal signals of negative polarity discussed in the present study requires caution considering differences in recording techniques such as position of the reference electrodes and filter bandwidths, as well as species differences.

Depolarization of cells and axons in the inner retina.

The components of negative polarity generated in the proximal retina correspond to depolarization of dipole structures arranged predominantly in layers parallel to the retinal surface (amacrine cells, ganglion cells, axons of the ganglion cells). The respective field potentials with contributions from depolarization of Müller cells produce neg-

active waveforms. Depolarization of sagittally oriented dipoles are understood to cause the negative a-wave and the positive polarity of the b-wave, generated primarily by photoreceptor

cells and by ON-bipolar cells, respectively, and probably by their interaction with Müller cells. The negative polarity and configuration of the retinal responses to antidromic electrical stimulation

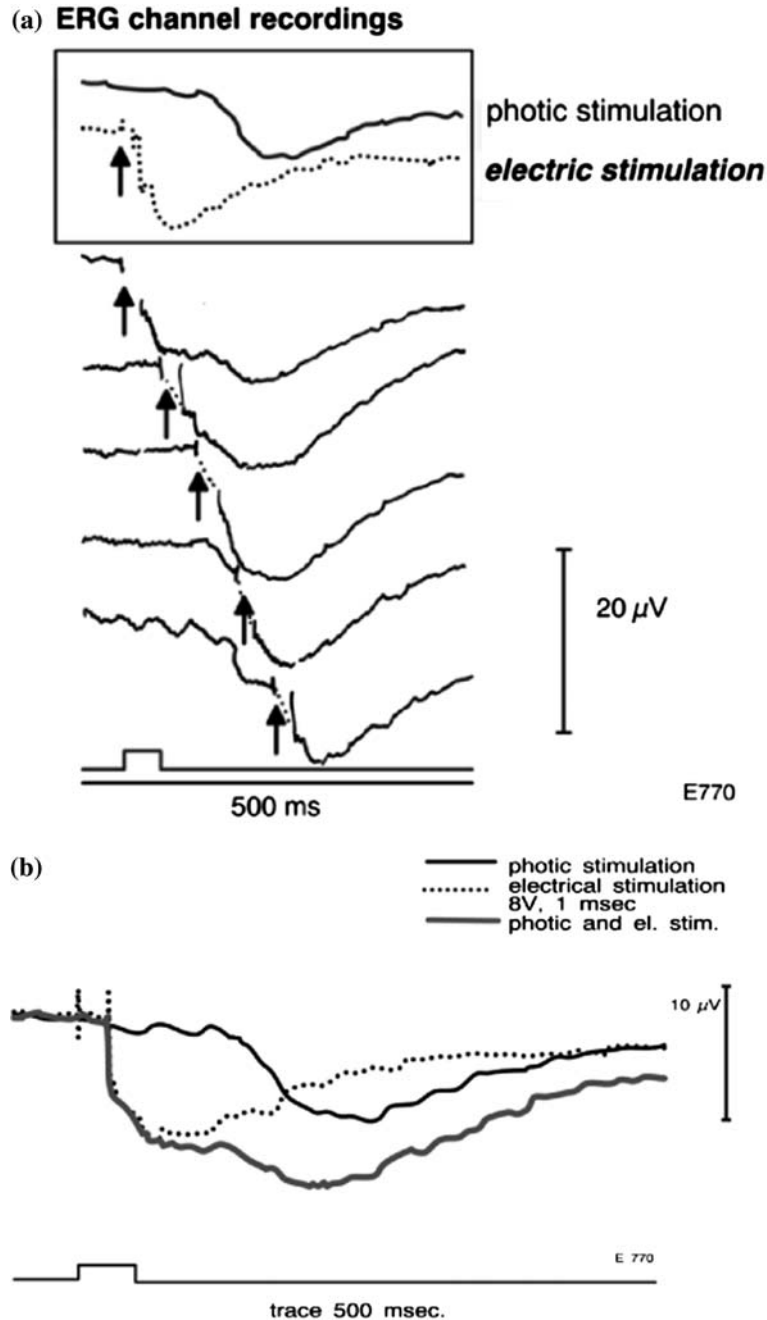


Figure 7. Traces from the ERG channel in perfused cat eyes revealing the light evoked STR as well as retinal negative potentials elicited by antidromic electrical stimulation of the optic nerve. (a) STRs elicited by the light pulse indicated by upward deflection of the trace at the bottom and electrically responses elicited at increasing delays as marked by the arrows. (b) Detailed display reveals the summation of the light evoked with the electrically elicited retinal signals [11].

of the optic nerve reported above supports this view: the generation of an STR-like field potential results from the activation of ganglion cells and probably from the depolarization of Müller cells [11].

Extensive electroencephalographic studies related to the issue of propagation of outspread excitatory signals of negative polarity to a distant recording site have been reviewed by Birbaumer et al. [53]: Excitatory postsynaptic potentials in cortical layer I exhibit current sinks that generate negative baseline shifts to the scalp. These slow potentials (latencies of >200 ms) occur under a number of clinical and experimental conditions may serve as an analogue for our understanding of the inner retinal excitatory signals of negative polarity as recorded from vitreous and cornea.

Summary

ERG components of negative polarity in the light-adapted and in the dark-adapted inner retina are reviewed from a clinical perspective and include consideration of experimental research. Field potentials are inherently complex including summing contributions from specialized neurons as well as from glial elements. This property applies to the PERG, PhNR and to the STR. Experimental research can contribute to identifying the sites/cells of origins i.e. by determining depth profiles and by pharmacological manipulation. Intraretinal microelectrode-studies and pharmacological dissection of light-evoked responses have elucidated the origin of field potentials from the retinal pigment epithelium to the retinal ganglion cells.

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